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# ORIGINAL ARTICLES

## Anatomic validation of a novel method for left ventricular volume and mass measurements with use of real-time 3-dimensional echocardiography

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**Assessment of left ventricular (LV) volumes and mass is a critical element in the evaluation of patients with cardiovascular disease. However, most non-invasive methods used for the quantitative measurements of LV volume and mass have important intrinsic limitations. Real-time 3-dimensional echocardiography (RT3D echo) is a new technique capable of acquiring volumetric images without cardiac or respiratory gating. The purpose of this study was to develop and validate a system for rapid LV volume and mass measurements with the use of RT3D echo images.**

**To this end, in 11 explanted sheep hearts, the left ventricle was instrumented with a latex balloon and filled with known volumes of saline solution. Two independent observers made volume calculations from images acquired with RT3D echo. In addition, 21 open-chest sheep were imaged with RT3D echo for LV mass calculation. Anatomic LV mass was determined after removing the heart. A strong correlation was observed between the actual LV volumes and those calculated from the RT3D echo images ($r = 0.99$; $y = 1.31 + 0.98x$; standard error of the estimate = 2.2 mL). An analysis of intraobserver and interobserver variabilities revealed high indexes of agreement. A strong correlation was observed between actual LV mass and that calculated from RT3D echo images ($r = 0.94$; $y = 14.4 + 0.89x$; standard error of the estimate = 8.5 gm). Thus RT3D echo images allow rapid and accurate measurements of LV volume and mass. This technique may expand the use of cardiac ultrasonography for the quantitative assessment of heart disease. (J Am Soc Echocardiog 2001;14:1-10.)**

The assessment of left ventricular (LV) size and function serves as an important predictor of cardiovascular morbidity and mortality, and thus aids the clinician in making decisions regarding patient care. For example, when evaluating patients with valvular or ischemic heart disease, measurements of LV volumes and ejection fraction are often used to determine the timing of valve replacement or coronary revascularization.[1] [5] Measurements of LV mass also offer additional prognostic information to that obtained by evaluation of traditional cardiovascular risk factors.[6] For example, in patients with coronary artery disease, left ventricular hypertrophy predicts an increased number of clinical events, including death,[7] and, in patients with essential hypertension, LV mass is more strongly associated with morbidity than blood pressure alone.[8] [9]

Cardiac ultrasonography techniques, including M-mode and 2-dimensional echocardiography, provide an excellent assessment of overall LV function and wall thickness. However, when assessing volume and mass, considerable variability exists between observers. Furthermore, LV volume and mass measurements with conventional echocardiography rely on geometric assumptions of uniform chamber size.[10] [14] Although this may be accurate for normal ventricles, it is inadequate for ventricles affected by disease. Thus this limitation is more obvious when most needed, such as in cases of distorted LV geometry (eg, aneurysm or asymmetric hypertrophy).

Three-dimensional echocardiography that uses reconstruction of 2-dimensional images has the ability to quantify LV volume in abnormally shaped ventricles.[15] [20] In addition, this method is accurate for measuring left and right ventricular mass, as well as for estimating infarct mass in patients with LV dysfunction.[21] [25] However, this technique involves acquisition of 2-dimensional images over several cardiac cycles with the use of spatial locators or rotational transducers to provide a computer with spatial information for subsequent reconstruction into a 3-dimensional format,[26] [27] a method that has found limited applications in routine clinical practice.

Real-time 3-dimensional echocardiography (RT3D echo) has recently become available for noninvasive imaging.[28] [30] This type of system is equipped with a matrix-array transducer capable of instantaneous acquisition and display of volumetric images without electrocardiographic or respiratory gating, thus permitting a true 4-dimensional assessment of cardiac structure and function. We have developed a method for rapid quantitative assessment of LV volume and mass with the use of RT3D echo images. The present study was designed to determine the accuracy and repeatability of this method by using animal models with known LV volume and mass.

## Methods

All operative and animal management procedures were approved by the Animal Care and Use Committee of the National Heart, Lung, and Blood Institute.

### *Animal preparation and imaging*

*Left ventricular volume study*

Eleven explanted sheep hearts were studied. Sheep underwent general anesthesia induced by sodium pentobarbital (25 mg/kg) and maintained with 2% isoflurane. After heparinization, each animal underwent a median sternotomy and was euthanized with an intravenous injection of KCl, as previously reported.[31] [32] The heart was immediately separated from the surrounding structures and placed on a bench. The left atrium was excised, and a latex balloon was positioned inside the LV chamber. Subsequently, the balloon was filled with 2 to 5 known amounts of saline solution, differing by approximately 10% to 20% of the initial volume. The RT3D echo images for each volume were acquired from the LV apex. A commercially available 3-cm gel pad (3M Medical-Surgical Division, St Paul, Minn) designed for ultrasonographic imaging was used as a standoff between the transducer and the LV apex. Images were saved on optical disks for later analysis. The time for image acquisition was approximately 2 to 5 minutes.

*Left ventricular mass study*

Twenty-one open-chest sheep were studied. General anesthesia was induced with sodium pentothal (25 mg/kg) and maintained with 2% isoflurane. After heparinization, each animal underwent a median sternotomy, as in the volume study. The RT3D echo images were acquired from the LV apex by using the same gel standoff pad. Acquisition time was 2 to 3 minutes. Each image was optimized with an attempt to include the entire endocardial and epicardial surface within the volumetric image. One cardiac cycle was stored on optical disk for later analysis. After image acquisition, each heart was removed from the thoracic cavity. The entire left ventricle was dissected from the remainder of the heart and weighed on a scale to determine LV mass.

### *RT3D echo imaging*

The methodology of RT3D echo imaging was first developed in the Center for Emerging Cardiovascular Technologies at Duke University and is based on the use of a 2-dimensional phased-array transducer consisting of a 43 × 43 element matrix. The system has been described in detail previously[28] [29] and has permitted the accurate determination of right ventricular stroke volume in animal studies.[30]

### *Measurements of LV volume and mass*

The RT3D echo images stored on optical disks were transferred to a separate workstation (Silicon Graphics, Inc, Mountain View, Calif) capable of high-resolution 3-dimensional volume rendering. The methodology for obtaining the LV ventricular surface and calculating LV volumes from volumetric images was specifically designed to visualize and produce instantaneous measurements. Therefore, the design of the system is based on the operator’s ability to trace and edit, if necessary, the endocardial surface on any arbitrary slice through the volumetric image and to reconstruct a visual rendering of the LV surface on the fly. This gives the operator immediate feedback as to how the rendered LV shape is

developing with each added data point. To this end, on the computer screen, images are presented in 2 simultaneously displayed formats: the slice view and the rendered view (Figure 1).

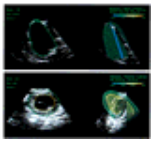

**Fig. 1.** Photographs taken directly from the computer monitor during calculation of left ventricular (LV) volume **(A)** and LV mass **(B)** with use of the interactively aided algorithm. In both panels, the slice view is shown on the *left* and the rendered view is shown on the *right*. The operator traces the LV surface on the slice view, and the computer instantaneously generates a mesh-like cast, which is displayed on the rendered view. Unlimited rotation of the slice view allows the observer to examine the correspondence between the computer-generated cast and the LV surface. In cases where the tracing does not faithfully follow the LV endocardial or epicardial surface, the operator can manually modify the tracing. In **B,** the *yellow line (left)* and cast *(right)* represent the endocardial surface, and the *green line (left)* and cast *(right)* represent the epicardial surface. (See text and Figures 2 and 3 for more details.)

The slice view allows the operator to trace the LV surface, which is viewed relative to the tomographic slice. The rendered view allows the tomographic slice to be viewed relative to the traced LV surface. This method interactively changes the geometry of the traced LV surface by observing the endocardial border on the slice view while viewing the entire surface on the rendered view. The slice view is always perpendicular to the viewing direction, and the traced LV surface is presented as a contour within the given slice. In the rendered view, the slice is embedded within the traced LV surface (Figure 1).

The algorithm uses a cylindrical surface representation and is able to handle sparse sampling points of the endocardial surface and then incorporate geometric characteristics of the left ventricle to compute values for the nonsampled areas of the surface, thus transforming a 3-dimensional reconstruction problem into a 2-dimensional interpolation problem. Geometric characteristics of the left ventricle can be easily represented and incorporated through the use of a 2-dimensional cylindrical surface representation. By using this type of structure, interpolation of the surface in the cylindrical coordinate domain provides curvature in the surface around the main axis, and the boundary conditions can be set up to close to a point at the apex to create a bullet-shaped 3-dimensional representation that fits the typical LV shape. A discrete representation of the surface is thus obtained, which is the projection of the LV surface onto a cylinder. The resultant 2-dimensional array of values, called a raster map, contains the radial distances from the main axis for a given angle and height. By formatting the unorganized set of points on a regular grid, the raster map provides a context within which point-to-point comparisons between 2 surfaces and the quantification of specific aspects of a surface can be calculated.

The process of reconstructing the LV surface from a set of endocardial wall points requires that the operator establish a ventricular coordinate system by selecting the apex, base, and lateral wall points of the left ventricle (Figure 2).

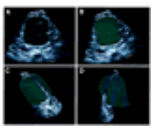

**Fig. 2.** Measurement of left ventricular (LV) volume from real-time 3-dimensional echocardiography images with use of the interactively aided tracing algorithm. On a single slice from the volumetric image, a coordinate system is established by defining the apex, base, and midventricular endocardium. The base point establishes the origin of the coordinate system; the apex establishes the direction of the *z*-axis and the scale of the coordinate system. In the slice view, the endocardial border is traced **(A)**, and a 3-dimensional cast representing the LV cavity is generated with corresponding volume calculation in the rendered view **(B)**. After the manual tracing of the endocardium is completed in one plane, the entire 3-dimensional image can be examined to determine proper matching between the computer-generated cast and the LV endocardium in all planes **(C)**. The *blue shaded areas* represent the regions traced by the observer, whereas the *green areas* represent the regions of the cast generated by the computer and not modified by the observer (**C** and **D**). The observer can trace the endocardial border in multiple planes until the computer-generated cast accurately represents the LV cavity.

Using the slice view, the operator makes a single long-axis tracing. As the operator traces the endocardial surface on the volumetric image, these data are instantaneously transformed into a cylindrical coordinate system and recorded on a 2-dimensional raster map. Values on the 2-dimensional raster map where data have not been recorded are interpolated with use of the available data. The LV surface is composed from the interpolated 2-dimensional raster map based on a cylindrical surface representation. To generate the initial rendered view, the algorithm assumes that the corresponding perpendicular short-axis sections have a symmetric circumference. The volumetric image can then be rotated in the slice view so that the computer-generated border can be examined and corrected (if necessary) to match the actual endocardial (or epicardial) border. This can be done repeatedly and in any plane until the observer is satisfied that the entire LV surface is accurately represented. Thus, all the 3-dimensional anatomic information contained in the volumetric image is incorporated in the final rendered view. A relatively normal ventricle may require relatively few corrections of the initial computer-generated tracing, whereas an abnormally shaped ventricle usually requires greater manual editing. The entire process of LV volume calculation takes approximately 2 to 5 minutes.

For calculation of LV mass, the endocardial and epicardial surfaces are traced, and the corresponding volumes are then subtracted to obtain the myocardial volume (Figure 3).

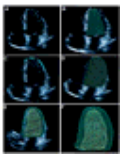

**Fig. 3.** Measurement of left ventricular (LV) mass with the use of real-time 3-dimensional echocardiography images with the interactively aided tracing algorithm. The end-diastolic frame is selected and a coordinate system is established by defining the apex, base, and midventricular endocardium, as described in Figure 2. In the slice view, the endocardial border is traced **(A)**, and a 3-dimensional cast representing the LV cavity is generated with corresponding volume calculation in the rendered view **(B)**. A separate coordinate system is created for the epicardial surface. The epicardial border is traced in the slice view **(C)**, and a 3-dimensional cast representing the epicardial surface is generated with the corresponding epicardial volume calculation in the rendered view **(D)**. The computer calculates the volume of myocardium by subtracting the endocardial volume from the epicardial volume (**E** and **F**). The myocardial volume is multiplied by the density of myocardium to determine LV mass. In **E** and **F**, the mesh-like casts represent the epicardial and endocardial surfaces, shown in *green* and *yellow*, respectively.

Once the process is completed, the rendered view provides a rotatable 3-dimensional visualization of the endocardial surface, from which the LV volume is calculated (Figure 2), or of both the endocardial and epicardial surfaces, from which the LV mass is calculated (Figure 3).

For the purpose of this study, LV volume calculations were made by 2 independent observers who were unaware of the true LV volume and of the other observer's measurement. In addition, each volume measurement was repeated at least 1 week later by 1 observer to allow subsequent assessment of intraobserver variability. A single observer, blinded to the anatomic data, performed the measurements of LV mass from the volumetric frame that showed the largest LV cavity size. Left ventricular mass was determined by multiplying the myocardial volume, calculated as described above, by a conversion factor of 1.05 gm/mL, which corresponds to the density of the myocardium.

### *Statistical analysis*

Data are presented as mean ± SD. Two means were compared by paired Student *t* test. Relations between 2 variables were assessed by means of Pearson's correlation coefficient and by linear regression analysis. Accuracy of RT3D echo for prediction of anatomic volume and mass was calculated by the root-mean-square percent error method.[24] Intraobserver and interobserver variabilities were assessed by using standard formulae.[24] The method of Bland and Altman[33] was used to assess agreement between 2 measurements. Because the true value of LV volume and mass was available in our study, the true

value (instead of the average value) was plotted in the *x*-axis.

## Results

### *Left ventricular volume study*

A total of 52 LV volumes, ranging from 38 to 120 mL, were obtained in the 11 sheep hearts studied (50 volumes were obtained from 10 sheep hearts, whereas 2 volumes were obtained from the remaining heart). A strong correlation was observed between the actual LV volumes and those calculated from the RT3D echo images ($r = 0.99$) (Figure 4).

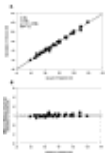

**Fig. 4.** Relation between actual left ventricular (LV) volume and real-time 3-dimensional echocardiography (RT3D echo) volume. **A,** Correlation between actual and calculated volume. **B,** Bland and Altman plot of the difference between actual and RT3D echo LV volumes as a function of the true value. Values above zero represent instances where RT3D echo volume was greater than the actual volume. The *solid* and *dashed lines* represent the mean ± 2 SD of the difference, respectively.

The mean difference was 2 ± 2 mL. The root-mean-square percent error was 3.04%.

Intraobserver variability was 7.61% with a mean absolute difference of 4 ± 4 mL. A strong correlation was observed between the two measurements ($r = 0.98$; $y = 0.52 + 1.04x$; standard error of the estimate [SEE] = 4.2 mL). Similarly, a high index of agreement was found between RT3D echo-derived LV volume measurements by 2 independent observers. Interobserver variability was 9.62%, with a mean difference of 6 ± 4 mL ($r = 0.97$; $y = 14.6 + 0.85x$; SEE = 5.1 mL).

### *Left ventricular mass study*

Actual LV mass from 21 sheep ranged from 68 to 178 gm (mean 116 ± 27). A strong correlation was observed between actual LV mass obtained from anatomic measurements and that calculated from RT3D echo images ($r = 0.94$) (Figure 5).

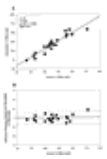

**Fig. 5.** Relation between actual left ventricular (LV) mass and real-time 3-dimensional echocardiography (RT3D echo) mass. **A,** Correlation between actual and calculated mass. **B,** Bland and Altman plot of the difference between actual and RT3D echo LV mass as a function of the true value. Values above zero represent instances where RT3D echo mass was greater than actual mass. The solid and dashed lines represent the mean ± 2 SD of the difference, respectively.

The mean absolute difference between actual and calculated LV mass was 7 ± 5 g. The root-mean-square percent error was 7.72%.

## Discussion

In the present study, we sought to determine whether a computerized method that permits rapid volumetric measurements can indeed provide accurate estimations of LV volume and mass from images obtained with RT3D echo. To ascertain appropriate validation of the measurements derived from this new technique, we used animal models to obtain true values of LV volume and mass. These measurements are obviously not possible in human studies because a different methodology must be

used as a reference standard, which in turn will have its own limitations and sources of inaccuracies. The study results demonstrate that computerized measurements of LV volume and mass from RT3D echo images accurately predict the actual anatomic values. In addition, LV volume measurements obtained with RT3D echo are highly reproducible as demonstrated by analysis of intraobserver and interobserver variabilities.

Although conventional M-mode and 2-dimensional echocardiography also offer the possibility of estimating LV volumes and mass,[34] [35] these measurements are unfortunately less accurate in those clinical situations in which they are more relevant for patient management, such as in patients with deformed LV geometry (eg, aneurysms or regional wall motion abnormalities) or asymmetric LV hypertrophy. Previous studies using reconstruction of transthoracic or transesophageal images have shown that 3-dimensional echocardiography provides more accurate quantification of LV volume and mass than can be obtained with 2-dimensional echocardiography.[15] [20] [23] [27] [36] [37]

The accuracy of RT3D echo measurements is comparable to 3-dimensional reconstruction methods. For example, in a study using excised canine ventricles filled with agarose, investigators found an average difference of 4.6 mL between the true value and that obtained with reconstructed 3-dimensional echocardiography, with an interobserver variability of 5.6%.[15] Another study using canine ventricles instrumented with a latex balloon found an average difference of 3.1 mL with an interobserver variability of 6.0%.[37] In our study, RT3D echo volume calculations had an average difference of 2 mL with an interobserver variability of 9.6%. Left ventricular mass measurements by RT3D echo also have a similar accuracy when compared with 3-dimensional reconstruction methods. Thus 2 previous studies using the latter method found a root-mean-square percent error of 3.5% and 6.8%.[24] [25] The RT3D echo measurements had a root-mean-square percent error of 7.7% for LV mass.

Although real-time and reconstruction 3-dimensional echocardiography have similar accuracy for calculation of LV volumes and mass, the latter method requires cardiac and respiratory gating for proper alignment of sequentially acquired images. Approximately 6 to 8 minutes are usually needed for image acquisition, and a minimum of 20 to 25 minutes are necessary for image reconstruction and analysis of LV volume or mass.[16] [24] [25] These factors have limited the use of this technique in routine clinical practice. In contrast, RT3D echo does not require gated acquisition and, in this regard, is not different from the familiar conventional real-time 2-dimensional echocardiography. In addition, complete volumetric images can be acquired within a few minutes. Left ventricular volume and mass measurements can be obtained within 5 minutes, a significantly shorter time period than that required for reconstruction methods. Thus RT3D echo constitutes an advance beyond 3-dimensional reconstruction echocardiography because it allows easy acquisition of images and rapid quantitative measurements.

In the present study, calculations of LV volume and mass were performed on a separate workstation with the use of specialized software. This software was specifically developed to allow rapid measurements from RT3D echo volumetric images and to take into account the need for unlimited feedback from the observer to modify the computer-generated tracing as necessary. The final LV endocardial and epicardial surfaces (from which volume and mass measurements are derived) is ultimately the result of the observer’s modifications to the initial rendering generated by the computer after the observer establishes easily identifiable landmarks. This interactive technique thus combines the advantages of high-speed computer graphics algorithms and the human eye’s ability to match the computer-generated tracing to the actual LV surface. In addition, because the volumetric images can be visualized on a single frame or in a dynamic cineloop format during the measurements, the observer can use the visual information derived from endocardial motion to more accurately identify the endocardial

surface at any point during the cardiac cycle.

It must be noted that although both LV volume and mass measurements were highly accurate, a greater variability existed in the mass measurements. Two reasons may account for this observation: (1) mass calculation requires measuring both endocardial and epicardial volumes, which introduces 2 potential sources of error as opposed to only 1 during volume calculation, and (2) acquisition of the entire epicardial surface may be difficult in some cases, particularly in patients with enlarged left ventricles, thus requiring extrapolation of part of the epicardial volume tracings by the observer.

Certain limitations of the RT3D echo system and of the design of our study must also be noted. First, compared with images obtained with commercially available 2-dimensional echocardiography machines, the RT3D echo images have a lower resolution, which could result in difficulties tracing the endocardial border when making LV volume calculations and thus limit their use in patients with suboptimal ultrasound windows. Also, in contrast to the 90° sector angle of 2-dimensional echocardiography systems, the RT3D echo image is limited to a 64° pyramidal volume, which may prevent imaging of the entire left ventricle in patients with significant LV enlargement or hypertrophy and thus affect the volumetric measurements. This is particularly true when making mass measurements because the epicardial apex can be difficult to image in cases of LV enlargement, which may reduce the accuracy of the calculation. Finally, we acknowledge that our study results refer to measurements obtained in animal models under ideal conditions; for example, the use of a distended latex balloon inside the left ventricle may flatten endocardial trabeculations and result in a smoother endocardial surface, which does not resemble the human left ventricle in vivo. Therefore, the present findings should be viewed as a proof of concept and not as a direct demonstration of the clinical usefulness of the methodology described herein.

In conclusion, this study indicates that RT3D echo images allow rapid and accurate measurements of LV volume and mass. This technique may thus enhance both the ability of noninvasive cardiac ultrasonography to provide a faithful quantitative functional assessment of heart disease and the response to diagnostic and therapeutic interventions.

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